PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Kazuhiro TERAI, et al.

Docket No.: Q85292

Appln. No.: 10/519,353

Group Art Unit: Not yet assigned

Confirmation No.: Not yet assigned

Examiner: Not yet assigned

Filed: December 28, 2004

For: AGENT FOR TREATING CEREBRAL HEMORRHAGE

INFORMATION DISCLOSURE STATEMENT
UNDER 37 C.F.R. §§ 1.97 and 1.98

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the duty of disclosure under 37 C.F.R. § 1.56, Applicant hereby notifies the U.S. Patent and Trademark Office of the documents which are listed on the attached PTO/SB/08 A & B (modified) form and/or listed herein and which the Examiner may deem material to patentability of the claims of the above-identified application.

One copy of each of the listed documents is submitted herewith, except for the following: U.S. patents and/or U.S. patent publications; and co-pending non-provisional U.S. applications filed after June 30, 2003.

The present Information Disclosure Statement is being filed: (1) No later than three months from the application's filing date; (2) Before the mailing date of the first Office Action on the merits (whichever is later); or (3) Before the mailing date of the first Office Action after

filing a request for continued examination (RCE) under §1.114, and therefore, no Statement under 37 C.F.R. § 1.97(e) or fee under 37 C.F.R. § 1.17(p) is required.

In compliance with the concise explanation requirement under 37 C.F.R. § 1.98(a)(3) for foreign language documents, Applicant encloses herewith a copy of the corresponding International Search Report indicating the degree of relevance found by the International Bureau. In addition, the following explanations of the foregin language documents are submitted:

1. Shindan to Chiryo (2001), 89(11): 2059-2064

This document is described in the specification at page 9. This document explains change of image findings of cerebral infarction. It is described that hemorrhagic transformation appears in infarction nest in examples of approximately 80% at a subacute stage of stroke, namely after 1 to 3 weeks from the onset of cerebral infarction.

2. Clinical Neuroscience 12(12): 29-32, 1994

This document is described in the specification at page 3.

3. Shindan to Chiryo (2001) 89(11):2017-2022

This document is described in the specification and was cited in the ISR and International Preliminary Examination Report ("IPER", hereinafter). This document explains that since a brain protecting drug such as an AMPA antagonist has activity against a tissue disorder due to ischemia-reperfusion, it also has activity of protection from a cerebrovascular disorder, and a possibility of its use in cerebral hemorrhage or the like is suggested. Partial English translations (Table 1 on page 2019, lines 7-14 of the right column of page 2020, from the last line of the right

column of page 2021 to line 8 of the left column of page 2022) are set forth below. A copy of Table 1 is attached herewith.

> 2) AMPA receptor inhibitor
>
> A possibility is suggested that when depolarization occurs by stimulation of an AMPA receptor, inflow of calcium via an NMDA channel is increased which leads to cytotoxicity. As a drug for protecting brain nerves by selective antagonism of this receptor, there is water soluble YM872, and a clinical trial thereof is currently under way.
>
> Further, these brain protecting drugs have been inherently developed for providing neuroprotective effect against cerebral ischemia. However, they have, unlike drugs used at an acute stage, such as an antiplatelet drug, an anticoagulant and a thrombolytic agent, activity against tissue disorders due to ischemia-reperfusion by migration into a brain tissue. Accordingly, they may be used in a wide-ranging region including not only cerebral infarction but also cerebral hemorrhage, traumatic brain damage, subarachnoid hemorrhage and the like.

4. JP-A-9-286727:

This document was cited in ISR and IPER. Partial English translations (abstract and paragraphs [0035] and [0036] of the specification) are set forth below.

> [Abstract]
>
> A glutamic acid antagonist containing theanine s an active ingredient, and a neuronal death preventing agent characterized by containing theanine as an active ingredient and having activity of blocking a glutamic acid receptor.
>
> [Advantange]
>
> Theanine can effectively inhibit toxicity of glutamic acid, stop spread of neuronal death and block on NMDA-type glutamic acid receptor. Further, theanine has characteristics that it is easily passed through a blood brain barrier and intestinal absorption is also high. Still further, it is a substance which is currently permitted as a food additive and daily taken in. Accordingly, theanine is effective for treatment and prevention of brain disorders caused by glutamic acid, for example, stroke such as cerebral infarction or cerebral hemorrhage and cerebral ischemia accompanied by brain operation or brain damage.
>
> [0035]
>
> [Advantage of the Invention]

In view of the foregoing results, when glutamic acid in the brain is notably increased due to cerebral ischemia or the like, the glutamic acid antagonist of the invention is administered to brain neurons by a method such as oral administration, administration in blood, direct administration or the like, whereby toxicity of glutamic acid can effectively be inhibited and late neuronal death caused by toxicity of glutamic acid flowed out from dead cells in particular can be inhibited to stop spread of neuronal death. Accordingly, it is effective for treatment of brain disorders caused by glutamic acid, for example, stroke such as cerebral infarction or cerebral hemorrhage and cerebral ischemia accompanied by brain operation or brain damage.

[0036]

The agent for preventing neuronal death in the invention can block an NMDA-type glutamic acid receptor and inhibit transmission of excess stimulus of glutamic acid to neurons to thereby prevent neuronal death. Accordingly, it is also effective for treatment of brain disorders caused by glutamic acid, for example, stroke such as cerebral infarction or cerebral hemorrhage and cerebral ischemia accompanied by brain operation or brain damage.

5. JP-A-8-59473:

This reference was cited in ISR and IPER. Partial English translations (abstract and paragraphs [0004] and [0012] of the specification) are set forth below.

[Abstract]

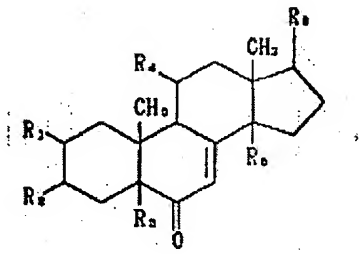
[Object]

To investigate a compound that inhibits brain neuronal death induced by glutamic acid and produce a cerebral neuroprotective agent effective for prevention or treatment of an ischemic brain disorder or the like.

[Construction]

A cerebral neuroprotective agent characterized by containing a compound represented by the following formula (I) as an active ingredient.

[Formula 1]



(I)

(wherein R_1 to R_5, independently from each other, represent a hydrogen atom or a hydroxyl group, and R_6 represents an alkyl group which may be substituted with a hydroxyl group.)

[0004]

However, most of the mechanism is still unknown. Despite much effort of investigation, drugs which are effective and satisfactory with high safety have not yet been found. Accordingly, the invention aims to investigate compounds that inhibit brain neuronal death induced by glutamic acid and to produce a brain neuroprotective agent effective for prevention or treatment of ischemic brain disorders and the like.

[0012]

Meanwhile, activity of protecting brain neurons as mentioned in the invention means inhibition of denaturation or necrosis of brain neurons accompanied by cerebral infraction caused by cerebral thrombosis, cerebral embolism, cerebrovascular twitch, abrupt blood pressure decrease, low perfusion blood vessel disease and the like, stroke caused by cerebral thrombosis, cerebral embolism, cerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, hypertensive encephalopathy and the like, brain damage, temporal stop of heartbeat, hypoxemia, hypoglycemia and the like. Further, it means inhibition of denaturation or necrosis of secondary brain neurons which gradually takes place after primary infarction such as cerebral infarction to induce dementia, mental disorder, behavioral disorder and the like.

6. WO 00/43006:

This reference was cited in ISR and IPER. Partial English translations (abstract and lines 6-15 of page 11 of the specification) are set forth below.

[Abstract]

Medicinal compositions for inhibiting neuronal death due to glutamic acid cytotoxicity which contain thiazolidindione compound as the active ingredient.

Neuronal death induces various diseases of a nervous system. Neuronal death is caused by activation of, for example, neurotoxicity (glutamic acid cytotoxicity) induced by glutamic acid or caspase (examples thereof can include caspase 3 and caspase 9). Especially, glutamic acid cytotoxicity is known to be a dangerous factor of both of apoptosis and necrosis, namely overall neuronal death.

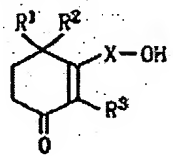
Examples of "diseases of a nervous system" in the foregoing description can include ischemic disorders (for example, stroke, cerebral hemorrhage and cerebral infarction), inflammatory brain diseases (for example, sequelae of encephalitis, acute meningitis, viral meningitis and vaccinal meningitis), neurodegeneration diseases (for example, Alzheimer disease, head injury, cerebral palsy, Huntington disease, Pick disease, Down syndrome, Parkinson disease, AIDS encephalopathy, multiple sclerosis, amyotrophic lateral sclerosis and cerebellar ataxia).

7. JP-A-2001-213771:

This reference was cited in ISR and IPER. Partial English translations (abstract, claim 2 and the paragraph [0003] of the specification) are set forth below.

[Abstract]
[Means for Resolution]

An agent for preventing or treating diseases based ona cerebrovascular disorder, the agent containing as an active ingredient a cyclohexene long-chain alcohol compound represented by formula (1)
[Formula 1]



(1)

[wherein R^1, R^2 and R^3 each represent H or CH_3, and X represents an alkylene group or an alkenyene group having from 10 to 28 carbon atoms].
[Advantage]

> Brain neurons are effectively protected from cerebrovascular disorders such as cerebral infarction.
> [Claim 2]
> The preventing or treating agent according to claim 1, wherein the cerebrovascular disorder is cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage or brain edema.
> [0003]
> Since the cerebrovascular disorder such as cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage or brain edema decreases blood flow in the brain, the brain falls into an ischemic condition. When the brain is in the ischemic condition, the glutamic acid concentration outside cells is increased, a postsynaptic glumatic acid receptor undergoes excess stimulus, and a calcium ion concentration in the cells is excessively increased to induce cytotoxicity. Neurons are then dropped to induce diseases such as dementia. Therefore, the in results of treating diseases based on the cerebrovascular disorder depends on how to conduct treatment at an acute state for protecting neurons and to what extent diseases can be improved at an acute stage. However, treating agents currently used in clinical treatment are an antiplatelet agent, an anticoagulant and the like, and they do not have activity of protecting nerves directly (No to Junkan 2, 13-17, 1997). It is known that after the treatment with an antiplatelet agent, an anticoagulant and the like, a stimulant such as NO is induced by reperfusion of blood to damage brain cells and cause nervous and mental diseases. Consequently, the development of agents for inhibiting excess increase in calcium ion concentration within cells or expediting discharge of the calcium ion for directly protecting neurons has been in demand.

8. WO 96/10023:

This reference is described in the specification. This reference was cited in the International Search Report (ISR, hereinafter) and the corresponding U.S. Patent is No. 6,096,743.

The submission of the listed documents is not intended as an admission that any such document constitutes prior art against the claims of the present application. Applicant does not

waive any right to take any action that would be appropriate to antedate or otherwise remove any listed document as a competent reference against the claims of the present application.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account. A duplicate copy of this paper is attached.

Respectfully submitted,

for Mark Boland #47,121
Registration No. 32,197

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 2

Complete if Known	
Application Number	10/519,353
Confirmation Number	Not yet assigned
Filing Date	December 28, 2004
First Named Inventor	Kazuhiro TERAI
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	Q85292

U.S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number: Number	Document Number: Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document
		US 6,096,743	A	08/01/2000	Shishikura et al.
		US			
		US			
		US			
		US			
		US			

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document: Country Code[3]	Number[4]	Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Translation[6]
		JP	9-286727	A	11/04/1997		No
		JP	8-59473	A	03/05/1996		No
		WO	00/43006	A1	07/27/2000		Abstract
		JP	2001-213771	A	08/07/2001		No
		WO	96/10023	A1	04/04/1996		Abstract

NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		Kazuhiro Terai et al., "Effect of AMPA receptor antagonist YM872 on cerebral hematoma size and neurological recovery in the intracerebral hemorrhage rat model", European Journal of Pharmacology (2003) Vol. 467, pp. 95-101	
		Kenichiro Katsura et al., "Nokosoku no Kyuseiki Chiryo to Nijiyobo Tokushu Chiryo-4 No Hogoyaku" (Shindan to Chiryo) (2001), Vol. 89, No. 11, pp. 2017-2022	
		Shindan to Chiryo (2001) Vol. 89, No. 11, pp. 2059-2064	
		Clinical Neurosscience (1994) Vol. 12, No. 12, pp. 29-32	
		Franciska Erdo et al., "Bimoclomol Protects Against Vascular Consequences of Experimental Subarachnoid Hemorrhage in Rats", Brain Research Bulletin (1998), Vol. 45, No. 2, pp. 163-166	
		Sachiko Kawasaki -Yatsugi et al., "Neuroprotective effects of an AMPA receptor antagonist YM872 in a rat transient middle cerebal artery occlusion model", Neuropharmacology (2000), Vol. 39, pp. 211-217	

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1]Applicant's unique citation designation number (optional). [2]See Kind Codes of USPTO Patent Documents at www.uspto.gov, MPEP 901.04 or in the comment box of this document. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST. 3). [4]For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5]Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. [6] Applicant is to indicate here if English language Translation is attached.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 2 of 2

Complete if Known	
Application Number	10/519,353
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First Named Inventor	Kazuhiro TERAI
Art Unit	Not yet assigned
Examiner Name	Not yet assigned
Attorney Docket Number	Q85292

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		US			
		US			
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		US			

FOREIGN PATENT DOCUMENTS

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NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city, and/or country where published.	Translation[6]
		Chao Gong et al., "Intracerebal Hemorrhage-induced Neuronal Death", Neurosurgery (2001), Vol. 48, No. 4, pp. 875-883	
		International Search Report dated August 26, 2003	

Examiner Signature		Date Considered	

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